General

Guideline Title

Systemic therapy of incurable gastroenteropancreatic neuroendocrine tumours.

Bibliographic Source(s)

Singh S, Sivajohanathan D, Asmis T, Cho C, Hammad N, Law C, Wong R, Zbuk K, Gastrointestinal Disease Site Group. Systemic therapy of incurable gastroenteropancreatic neuroendocrine tumours. Toronto (ON): Cancer Care Ontario (CCO); 2016 Dec 9. 70 p. (Program in Evidence-Based Care (PEBC); no. 2-21). [64 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Recommendation 1

Patients with well or moderately differentiated pancreatic neuroendocrine tumours (pNETs) should be offered targeted therapy (i.e., everolimus or sunitinib). No evidence-based recommendation can be made for or against other types of targeted therapy, somatostatin analogues, chemotherapy or combination therapy due to insufficient evidence.

Recommendation 2

Patients with non-pNETs should be offered either targeted therapy (i.e., everolimus) or somatostatin analogues (i.e., octreotide long-acting repeatable [LAR] or lanreotide). No evidence-based recommendation can be made for or against other types of targeted therapy, somatostatin analogs, chemotherapy, or combination therapy due to insufficient evidence.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Incurable gastroenteropancreatic (GEP) neuroendocrine tumours (NETs)
- Non-pancreatic neuroendocrine tumours (non-PNETs)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Endocrinology

Gastroenterology

Neurology

Oncology

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To make recommendations with respect to systemic therapy for the treatment of patients with incurable gastroenteropancreatic (GEP) neuroendocrine tumours (NETs) or non-pancreatic NETs

Target Population

Adults with a diagnosis of incurable gastroenteropancreatic (GEP) neuroendocrine tumours (NETs) or non-pancreatic NETs

Interventions and Practices Considered

1. Targeted therapy with everolimus or sunitinib for patients with incurable gastroenteropancreatic neuroendocrine tumours (NETs)
2. Everolimus or somatostatin analogues (SSAs; octreotide long-acting repeatable [LAR] or lanreotide) for patients with non-pancreatic NETs

Note: The following were considered but not recommended due to insufficient evidence: other types of targeted therapy, chemotherapy,

combination therapy.

Major Outcomes Considered

- Overall survival (OS)
- Progression-free survival (PFS)
- Objective response rate (ORR)
- Median survival time
- Quality of life
- Adverse effects

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

> Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
>
> Guideline developer Web sites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and the National Health and Medical Research Council - Australia.

The following criteria were used to select potentially relevant guidelines:

> Guideline databases and Web sites were searched using the following keyword "neuroendocrine." Only evidence-based guidelines published after 2010 (i.e., less than five years old) were considered.

This search did not yield a guideline that could be adapted or endorsed.

Methods

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. This included original systematic reviews and systematic reviews published as a component of practice guidelines. The MEDLINE (2008 to June 13, 2016) and EMBASE (2008 to June 13, 2016) databases, as well as the Cochrane Database of Systematic Reviews (2008 to June 13, 2016), Cancer Agencies for Drug and Technologies in Health (August 27, 2015) and Agency for Healthcare Research and Quality (August 27, 2015) were searched for published

systematic reviews. The full search strategy is available in Appendix 2 in the original guideline document.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool to determine whether or not it could be incorporated as part of the evidentiary base.

Search for Primary Literature

In the absence of any relevant systematic reviews, a search was conducted for primary literature.

The MEDLINE (2008 to June 13, 2016) and EMBASE (2008 to June 13, 2016) databases were searched for published phase II and III randomized controlled trials (RCTs) and non-RCTs. The full search strategy is available in Appendix 2 in the original guideline document. Reference lists of included primary literature were scanned for additional citations. The following conference proceedings were also searched from 2008 to 2015: ASCO, ASCO Gastrointestinal Cancers Symposium, European Society for Medical Oncology, European Cancer Congress, European Neuroendocrine Tumour Society, and North American Neuroendocrine Tumour Society.

Study Selection Criteria and Process

Inclusion Criteria

- Prospective (phase II and III) and retrospective studies with ≥20 participants
- Studies assessing adult patients with incurable gastroenteropancreatic (GEP) neuroendocrine tumours (NETs). At least 80% of the patients evaluated for the outcomes in each study should have GEP NETs as opposed to other types of NETs (e.g., lung, unknown primary, etc.)
- Studies that reported on or compared the effects of any of the systematic therapies (i.e., chemotherapy, somatostatin analogues [SSAs] or interferon α, and targeted therapies [i.e., sunitinib, everolimus, bevacizumab, pazopanib]) on any of the following clinical outcomes: progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and median survival, with or without biomarker decreases (i.e., chromogranin A, pancreastatin, glucagon), quality of life, and adverse effects

Exclusion Criteria

- Studies assessing the following conditions: pituitary tumours, large cell neuroendocrine carcinoma, thymic tumours, goblet cell carcinoma, bronchial NETs, paragangliomas, mixed NETs, pheochromocytoma, small cell lung cancer, and thyroid cancer
- Abstracts of non-randomized studies (single-arm clinical trials, case series, etc.)
- Abstracts of interim analyses
- Papers or abstracts not available in English
- Letters and editorials that reported clinical trial outcomes
- Papers and abstracts published before 2008

A review of the titles and abstracts that resulted from the search was conducted by one reviewer. For items that warranted full-text review, the same reviewer reviewed each item.

Refer to the "Results" section of the original guideline document for information on studies retrieved through the literature searches.

Number of Source Documents

Existing Guidelines: No relevant guidelines were identified.

Existing Systematic Reviews: No relevant systematic reviews were identified.

Primary Literature: 40 studies were included.

See also the PRISMA flow diagram in Appendix 3 of the original guideline document.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

The overall quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was conducted by one reviewer and audited by a second independent auditor. Ratios, including hazard ratios (HRs), were expressed with a ratio <1.0 indicating improved efficacy for the experimental arm. Important risks of bias, such as statistical power calculations, sample size, methods of randomization, allocation concealment, blinding, intention to treat analysis, and source of funding were extracted for each randomized study. Criteria from the ROBINS-I tool were used to assess the risk of bias for all non-randomized studies.

Criteria from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method were used to assess the quality of the aggregate evidence for randomized controlled trials (RCTs) and non-RCTs. Four factors were assessed for each outcome in each comparison: risk of bias, inconsistency, indirectness, and imprecision.

Synthesizing the Evidence

A meta-analysis was not planned due to the heterogeneity across trials and the inclusion of a large number of single-arm studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Developers

This guideline was developed by the Gastrointestinal Disease Site Group (GI DSG) (see Appendix 1 in the original guideline document), which was convened at the request of the Disease Pathway Management Group. The project was led by a small Working Group of the GI DSG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in radiation oncology, medical oncology, surgery, and health research methodology. Other members of the GI DSG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group.

Guideline Development Methods

The Program in Evidence-Based Care (PEBC) produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle. This process includes a systematic review, interpretation of the evidence by the Working Group, draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the Appraisal of Guidelines Research and Evaluation (AGREE) II framework as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the PEBC Document Assessment and Review Protocol (see the "Availability of Companion Documents" field). PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the PEBC Handbook and the PEBC Methods Handbook (see the "Availability of Companion Documents" field).

Research Question

Which of the anti-neoplastic systemic therapies (i.e., chemotherapy, somatostatin analogues [SSAs] and interferon α, and targeted therapies [i.e., sunitinib, everolimus, bevacizumab, pazopanib]) is the most effective in improving clinical outcomes (i.e., progression-free survival [PFS], overall survival [OS], objective response rate [ORR], median survival, symptom control, biomarker decreases, quality of life) while minimizing adverse effects (i.e., toxicity) in patients with incurable gastroenteropancreatic (GEP) neuroendocrine tumours (NETs)?

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the Guideline Development Group (GDG) Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the Program in Evidence-based Care (PEBC) Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the

revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

Patient- and Caregiver-Specific Consultation Group

Four patients/survivors/caregivers participated as Consultation Group members. They reviewed the draft recommendations and provided feedback on its comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

See Section 5 in the original guideline document for further discussion of the internal and external guideline review process and results.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized and non-randomized prospective studies and retrospective studies.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- The desirable effect of targeted therapy with everolimus or sunitinib (i.e., increased progression-free survival [PFS]) on incurable gastroenteropancreatic neuroendocrine tumours (NETs) is considerable, while the undesirable effects (i.e., adverse events) are acceptable for targeted therapy.
- The desirable effect (i.e., increased PFS) on non-pancreatic NETs is large for both everolimus and octreotide, while the undesirable effects (i.e., adverse events) are small. The Working Group believes the desirable effect is large relative to the undesirable effect.

Potential Harms

Hematologic (e.g., anemia, neutropenia, leucopenia) and non-hematologic toxicities (e.g., diarrhea, vomiting, infections, anorexia) targeted therapy and somatostatin analogues (SSAs). See Table 4-4 and the "Adverse Events" sections in the original guideline document for additional information on potential harms.

Qualifying Statements

Qualifying Statements

- Care has been taken in the preparation of the information contained in this report. Nevertheless, any person seeking to consult the report or apply its recommendations is expected to use independent medical judgment in the context of individual clinical circumstances or to seek out the supervision of a qualified clinician. Cancer Care Ontario (CCO) makes no representations or guarantees of any kind whatsoever regarding the report content or its use or application and disclaims any responsibility for its use or application in any way.
- See the original guideline document for qualifying statements related to each recommendation.

Implementation of the Guideline

Description of Implementation Strategy

Implementation Considerations

The Working Group considered these recommendations to be the best possible recommendations given the currently available data and their feasibility of implementation. Research has shown that patients in rural settings have poorer outcomes and standardizing care would reduce this inequity. These recommendations would validate and align with what providers are currently implementing. Funding of drugs for neuroendocrine tumours (NETs) must take into account the difficulty in conducting trials with homogeneous populations in this disease and the need to often have heterogeneous populations in order to feasibly assess new systemic therapies. Due to the limited number of cases, funding bodies must recognize that data obtained in the assessment of systemic therapy for NETs are unlikely to be the same level of quality as in other cancers. Accordingly, treatment options that have a biological rationale, such as the use of targeted therapy in the second-line treatment of pancreatic NETs (pNETs), should be considered. The Working Group believed the outcomes valued in this guideline would align with patient values and that patients would view these recommendations as acceptable.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Singh S, Sivajohanathan D, Asmis T, Cho C, Hammad N, Law C, Wong R, Zbuk K, Gastrointestinal Disease Site Group. Systemic therapy of incurable gastroenteropancreatic neuroendocrine tumours. Toronto (ON): Cancer Care Ontario (CCO); 2016 Dec 9. 70 p. (Program in Evidence-Based Care (PEBC); no. 2-21). [64 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Dec 9

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario (CCO) supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Systemic Therapy of Incurable Gastroenteropancreatic Neuroendocrine Tumours Working Group

Gastrointestinal Disease Site Group

Composition of Group That Authored the Guideline

Authors: S. Singh, D. Sivajohanathan, T. Asmis, C. Cho, N. Hammad, C. Law, R. Wong, K. Zbuk

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-Based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, and internal and external reviewers were asked to disclose potential conflicts of interest. The COI declared did not disqualify any individuals from performing their designated role in the development of this guideline.

See Appendix 1 in the original guideline document for information on authors' affiliations and conflict of interest declarations.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Cancer Care Ontario (CCO) Web site .

Availability of Companion Documents

The following are available:

Systemic therapy of incurable gastroenteropancreatic neuroendocrine tumours. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2016 Dec 9. 5 p. Available from the Cancer Care Ontario (CCO) Web site .

Program in Evidence-based Care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Available from the CCO Web site .

Program in Evidence-based Care methods handbook. Toronto (ON): Cancer Care Ontario (CCO); 2014 Sep 23. Available from the Program in Evidence-based Care (PEBC) Toolkit Web site .

Program in Evidence-based Care document assessment and review protocol. Toronto (ON): Cancer Care Ontario (CCO); 2015 Apr 16. 15 p. Available from the CCO Web site .

Patient Resources

None available

NGC Status

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